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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/671,953	09/27/2000	Claude Meares	2307O-099120US	8313

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TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER
HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/671,953	Applicant(s) MEARES ET AL.	
	Examiner Larry R. Helms	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,10,11,14-25,30-38,42 and 43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *10 and 11* is/are allowed.

6)☒ Claim(s) *1-3,14-25,30-38,42 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 October 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

1. Claims 1-3, 10-11, 14-25, 30-38 are pending.

Claims 39-41 were cancelled and claims 42-43 were added and claims 1, 10, 18, and 25 were amended in the amendment filed 10/7/02

2. Claims 1-3, 10-11, 14-25, 30-38 are under examination.

3. The text of those sections of Title 35 U.S.C. code not included in this office action can be foound in a prior Office Action

Rejection Withdrawn

4. The rejection of claims 1-3, 14-25, 30-38 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of arguments and amendments to the claims.

Response to Arguments

Specification

5. The objection to the disclosure is maintained because of the following informalities:

a. The disclosure is objected to because on page 1, lines 19-20 contains embedded hyperlinks and/or other form of browser-executable code. Applicant is

required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

the response filed 10/7/02 has been carefully considured but is deemed not to be persuasive. The response did amend the specification, however, it appears that the same material removed in the amendment was added back in and thus does not correct the hyperlink (see page 1-2 of response and marked up copy on page 15 of response).

6. The rejection of claim 14 under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description is maintained.

The response filed 10/7/02 and the response filed 10/28/02 have both been carefully considured but are deemed not to be persuasive. The response filed 10/7/02 stats that the deposit of cell line expressing the S95C antibody is being deposited with the ATCC (see page 8 of response of 10/7/02) and the response filed 10/28/02 provided evidence that the cell line expressing the S95C antibody was deposited and all conditions met for deposit (see response filed 10/28/02). In response to these arguments, claim 14 recites "The mutant antibody according to claim 1, wherein said mutant antibody is a mutant of CHA255". While the deposited antibody is a mutant of the CHA255 antibody, the claim recites a genus of antibodies not just the species of S95C. The claim requires the CHA255 antibody in order to practice the invention. The

claim requires a mutant of CHA255 which encompasses a genus of mutants. This rejection would be obviated by either reciting in the claim the antibody of claim 1 wherein the antibody is S95C and the deposit number from the ATCC for this cell line or depositing the CHA255 antibody cell line.

7. The rejection of claims 1-3, 14-25, 30-38, and newly added claims 42-43 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mutant antibody that comprises a reactive site not present in the wild type parent antibody wherein the mutant antibody comprises 6 CDRs and specifically binds to a metal chelate wherein the reactive site is in a position proximate to or within a CDR, does not reasonably provide enablement for a mutant antibody that does not comprise a full set of 6 CDRs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims is maintained.

The response filed 10/7/02 has been carefully considured but is deemed not to be persuasive. The response states that on page 11 of the specification "a CDR refers to the part of the antibody that recognizes the target or portions thereof" and it is known in the art that portions of the variable region of antibodies are responsible for target recognition and cites Paul as a reference and the specification provides ample guidance to make antibody fragments (see page 6 of the response). In response to these arguments, it is not disputed that Paul teaches and the specification discloses CDRs are parts of antibodies that bind antigen or that the specification discloses antibody

fragments. What is at issue is that the specification as well as Paul does not teach antigen binding fragments that do not contain a full set of CDRs from both a heavy and light chain as broadly encompassed by the claims. The specification as well as Paul does not teach antigen binding with a single CDR as encompassed by the claims.

The response further states that the examiner has mischaracterized the disclosure of Rudikoff et al and states that Rudikoff et al supports the proposal that amino acid substitutions may be made in antibodies without affecting antigen binding (see page 7 of response). In response to this argument, the examiner states that Rudikoff et al does teach amino acid substitutions in the CDRs of an antibody alter the antigen binding specificity (see title and abstract). While it is true that some substitutions outside the CDRs can be made in an antibody without altering the antigen binding, it is art known that an antibody needs a full set of CDRs for antigen binding and the claims encompass antibodies without a full set of CDRs.

8. The rejection of claims 1-3, 14, 16-19, 24 and newly added claim 42 under 35 U.S.C. 102(b) as being anticipated by Stickney et al (Cancer Research 51:6650-6655, 1991, IDS #7) is maintained.

The response filed 10/7/02 has been carefully considured but is deemed not to be persuasive. The response states that "the antibody of Stickney et al does not have any reactive site. Thus, Stickney et al does not disclose an antibody having a reactive site that is a free sulfhydryl group as disclosed and claimed" (see page 9 of response). In response to this argument, Stickney et al does have a reactive site in the

linker because the linker is a bis-maleimidomethyl ether and the linker would be a reactive site for acids, for example. The claims require a reactive site and the art of Stickney teach a linker with a reactive site. As far as the reactive site of a SH group is concerned the specification does not specifically define a "reactive site" and the claims are read in the broadest interpretation and the SH group is still available as a reaction site with DTT or a reducing agent. The claims do not require the SH group to be a group still available for a reaction.

Amending the claims to require an antibody wherein the antibody binds a metal chelate wherein said antibody has a SH group proximate to a CDR which is not present in the wildtype antibody and wherein the SH group forms a covalent bond with a reactive group on the chelate when bound to the antibody would obviate this rejection.

9. The rejection of claims 1-3, 14, 16, 17, 18, 19, 20, 22, 23, 25, 30, 31, 32, 33, 34, 37, 38, and newly added claims 42-43 under 35 U.S.C. 103(a) as being unpatentable over Reardan et al (Nature 316:265-267, 1985, IDS #7) and further in view of Orlandi et al (Proc. Natl. Acad. Sci. USA 86:3833-3837, 1989) and Pastan et al (U.S. Patent 5,747,654, issued 5/5/98, IDS #8) and Goodwin et al (The Journal of nuclear medicine 29:226-234, 1988, IDS #7) is maintained.

The response filed 10/7/02 has been carefully considered but is deemed not to be persuasive. The response states that the combination of references fails to disclose each element of the claimed invention and the response then addresses each reference

(see page 11 of response). The response states that Reardan et al does not suggest a mutant antibody comprising a reactive site not in the wild-type antibody and Orlandi et al does not suggest a reactive site and Pastan et al does not suggest that the disulfide stabilized antibody comprises a reactive group and Goodwin et al does not suggest a mutant antibody comprising a reactive site and the antibody of Goodwin et al does not bind a chelate comprising a reactive functional group of complementary reactivity to the reactive site (see pages 11-12 of response). In response to these arguments, Pastan et al clearly teaches a disulfide stabilized antibody and the antibody comprises a SH group not present in the wildtype antibody. As stated above, the claims require a "reactive site" and the disulfide stabilized antibody has a reactive group because the disulfide bond would react with a reducing agent. With regard to Goodwin et al Goodwin et al clearly teaches a chelate comprising a reactive functional group of complementary reactivity to the reactive site (see figure 1). In addition, it appears as though the arguments are directed to the references separately and this rejection is based on a combination of references.

The response states that there is no motivation to combine the references and the rejection is based on hindsight (see page 12 of response). In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only

from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). It would have been obvious to produce the claimed invention because Pastan et al teaches the antibodies can be stabilized for greater stability and have small size and reach there target more rapidly and cleared quicker for targeting and imaging application (see column 2, lines 49-55) and Goldwin et al antibody is used for imaging and it would have been obvious to stabilized Goodwin et al antibody by the method of Pastan et al for the reasons states by Pastan.

The response further states that one of skill in the art would not have a reasonable expectation of success to modify the references (see page 13 of response) and the prior art does not provide guidance regarding the placement of the reactive site, let alone in a position proximate to a CDR. In response to this argument, Pastan et al made several antibodies and they all were functional and this would lead one to conclude that it would be successful. In addition, Pastan et al teach the residues modified are proximate to a CDR (see column 5 where many of the residues are near a CDR, for example residue 100 and 44).

The response further states that the rejection of claims 17 and 31 is based on erroneous interpretation (see pages 13-14 of response) and the targeting moiety and the antibody are not the same. In response to this argument, there is nothing in the claims or the specification that requires the antibody and the targeting moiety to not be the same.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

10. Claims 10 and 11 are in condition for allowance.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of

this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

13. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879